Docket No.: 251732US0DIV

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
MARIA G. LUNTS, ET AL.	: EXAMINER: MARX, I.
SERIAL NO: 10/822,704	:
FILED: APRIL 13, 2004	: GROUP ART UNIT: 1651

FOR: BACTERIUM HAVING ABILITY TO PRODUCE L-GLUTAMIC ACID, L-PROLINE OR L-ARGININE AND METHOD FOR PRODUCING L-GLUTAMIC ACID, L-PROLINE OR L-ARGININE

APPEAL BRIEF

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

This is an appeal of twice-rejected Claims 5-12 in the above-identified application and the rejections set forth in the Official Action mailed August 9, 2007 and maintained in the Advisory Action mailed December 3, 2007.

I. Real Party of Interest

The real party of interest is Ajinomoto Co., Inc., by virtue of the assignment recorded in the U.S. Patent and Trademark Office on December 17, 2001, at reel 012371, frames 0690-0692.

II. Related Appeals and Interferences

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

However, Appellants' wish to bring to the Board's attention the fact that the following Appeals were previously filed: U.S. 08/890,199 (now U.S. 5,976,843), U.S. 09/307,450, U.S. 09/441,055, and U.S. 09/737,580 (now U.S. 6,682,912).

III. Status of Claims

Claims 5-12 are the only claims pending in the above-identified application and appear in the attached Claims Appendix. Original Claims 1-4 were canceled by Preliminary Amendment filed at the outset of prosecution of this application.

No claims have been identified as allowed or confirmed.

No claims have been identified as withdrawn. However, the claims as presented have only been examined to the extent that they read on production and accumulation of L-glutamic acid by virtue of the election of species made on December 28, 2006, in response to the Election of Species Requirement mailed on September 13, 2006.

No claims have been identified as objected to.

Claims 5-12 stand rejected.

Claims 5-12 are appealed herein.

IV. Status of Amendments filed under 37 C.F.R. §1.116

An Amendment under 37 C.F.R. §1.116 was not filed. The Request for Reconsideration, filed November 9, 2007, was considered by the Examiner and deemed not

to be persuasive to the allowance of Claims 5-8 under 35 U.S.C. §102(b) over Phillips et al in view of Integrated Enzyme Database and Claims 9-12 under 35 U.S.C. §103(a) over Phillips et al in view of Integrated Enzyme Database and further in view of Kinoshita et al. As such, an Advisory Action was issued on December 3, 2007. Appellants now appeal the rejections set forth in the Office Action mailed August 9, 2007, and maintained in the Advisory Action mailed on December 3, 2007. Claims 5-8 have been at least twice rejected.

V. Summary of the Claimed Subject Matter

As recited in independent Claim 1, the present invention provides a method for producing L-glutamic acid, L-proline or L-arginine by culturing an *Escherichia* bacterium, which is L-isoleucine auxotrophic and has ability to produce L-glutamic acid, L-proline or L-arginine, in a medium containing L-isoleucine, to produce and accumulate L-glutamic acid, L-proline or L-arginine in a culture and collecting L-glutamic acid, L-proline or L-arginine from the culture (see the specification at page 2, line 19 to page 3, line 6 and page 9, line 10 to page 10, lines 21). Appellants specifically direct the Board's attention to the description of the claimed method at page 9, line 10 to page 10, line 21.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Claims 5-8 stand rejected under 35 U.S.C. §102(b) over Phillips et al[1] in view of Integrated Enzyme Database[2].
2. Claims 9-12 stand rejected under 35 U.S.C. §103(a) over Phillips et al[3] in view of Integrated Enzyme Database[4] and further in view of Kinoshita et al[5].

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[1] J. Bacteriology, Feb. 1972, vol. 109, pp. 714-491.
[2] http://www.ebi.ac.uk/intenz/query?cmd+SearchEc&ec=4.3.1.19, accessed 2/8/07.
[3] See FN-1.
[4] See FN-2.

VII. Arguments

(A) Claims 5-8 stand rejected under 35 U.S.C. §102(b) over Phillips et al in view of Integrated Enzyme Database. This rejection is untenable and should not be sustained.

In the Office Action mailed August 9, 2007, the Examiner attempts to remedy the past insufficiency in making this rejection due to the failure to indicate where (page and line or figure) such a teaching or suggestion appears in the prior art[6] to support the allegation that the "strain *Escherichia coli* LA-9 clearly produces L-glutamic acid which is collected from the culture." In response, the Examiner offers:

> "Regarding the collecting step, in order to present the graphs in figure 1, clearly the glutamate is collected from the culture together with the cells to construct the growth curves, i.e., Curve 1, 2, 4, and 7."

However, when the growth curve is constructed, the absorbance of the culture is monitored. Indeed, Phillips et al specifically disclosed that the growth was monitored at 660 nm (see legend for Figure 1). If a sample (e.g., 1 ml aliquot) of the culture is removed to determine the absorbance at 660 nm, the sample is still in culture and is subjected to the absorbance determination as it is. In other words, the absorbance reading is a determination of the optical density of the culture. This does not constitute or require collection of the L-glutamic acid from the culture. Simply put, the skilled artisan would appreciate that the mere harvesting of cells (e.g., for determination of the optical density) is not the collection of L-glutamic acid from the culture as presently claimed.

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[5] U.S. 3,220,929

[6] When an Examiner maintains that there is an implicit teaching or suggestion in the prior art, "the Examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art." (*Ex parte* Jones, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001).

In the Advisory Action mailed December 3, 2007, the Examiner alleges that the arguments presented above are not persuasive and the rejection has been maintained. The Examiner's position with respect to the anticipation rejection is that "there is no clear definition of 'collecting L-glutamic acid, L-proline or L-arginine from the culture' [in the specification]". As such, the Examiner alleges the term "collecting" would broadly embrace an interpretation of the recited amino acids as well as cells.

Appellants disagree with Examiner's assertion and refer the Board to page 10, lines 18-21 of the specification that clearly defines the term "collection" stating:

> "Collection of L-glutamic acid, L-proline or L-arginine *from the culture* may be usually carried out by combining an ion exchange resin method, a precipitation method and other known methods."

Further, at page 10, lines 16-17, the term "culture" is defined as:

> "The culture includes a medium and cells, and is preferably a medium."

Thus, page 10, lines 18-21 of the specification should properly be read as:

> "Collection of L-glutamic acid, L-proline or L-arginine *from medium and cells, and preferably from a medium,* may be usually carried out by combining an ion exchange resin method, a precipitation method and other known methods."

Claim 5 as pending in this Appeal recites:

> A method for producing L-glutamic acid, L-proline or L-arginine by culturing an *Escherichia* bacterium, which is L-isoleucine auxotrophic and has ability to produce L-glutamic acid, L-proline or L-arginine, in a medium containing L-isoleucine, to produce and accumulate L-glutamic acid, L-proline or L-arginine in a culture and collecting L-glutamic acid, L-proline or L-arginine from the culture.

Therefore, when Claim 5 is read in context of the definitions provided on page 10, lines 16-21, the culture embraces both the cells and the medium. Accordingly, Appellants submit that, contrary to the Examiner's assertion, "collection" is clearly defined at page 10,

lines 16-21 and that when Claim 5 is reviewed accordingly would exclude the presence of the cells.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Clearly, Phillips et al fail to meet this requirement.

Additionally, Appellants submit that Phillips et al is silent about the production and accumulation of L-glutamic acid. Therefore, for this additional reason, Phillips et al do not anticipate the claimed invention. In the Advisory Action mailed December 3, 2007, the Examiner alleges:

> "[I]t is noted that there is nothing on this record to demonstrate that any *Escherichia* or any *E. coli* that is L-isoleucine auxotrophic will have the ability to produce L-glutamic acid (or L-proline or L-arginine) beyond a basal level as argued. The claims as written merely require any *Escherichia* or any *E. coli* to be L-isoleucine auxotrophic and to have the ability to produce L-glutamic acid (or L-proline or L-arginine). The amount produced is not required to be beyond a basal level."

Appellants disagree with this allegation by the Examiner noting that Claim 5 specifically requires "culturing an *Escherichia* bacterium... *to produce and accumulate* L-glutamic acid, L-proline or L-arginine in a culture" (*emphasis added*). As such, Appellants submit that the claims as presented *do* require expression beyond basal expression. Specifically, Appellants submit that it is well known that the amount of L-glutamic acid (or L-proline or L-arginine) produced by an *E. coli* cell is only that which is sufficient to survive (i.e., basal production). Thus, in order to accumulate L-glutamic acid (or L-proline or L-arginine) in the culture as required by the pending claims, it is necessary that the *Escherichia* bacterium produce L-glutamic acid (or L-proline or L-arginine) in excess of basal expression.

Moreover, as defined on page 3, lines 15-21 of the specification, Appellants define the expression "a bacterium has ability to produce L-glutamic acid, L-proline or L-arginine" as follows:

> The expression "a bacterium has ability to produce L-glutamic acid, L-proline or L-arginine" means that the bacterium accumulates a significant amount of L-glutamic acid, L-proline or L-arginine in a medium when the bacterium is cultured in the medium, or increases the content of L-glutamic acid, L-proline or L-arginine in the bacterium. The expression "a bacterium is L-isoleucine auxotrophic" means that the bacterium requires L-isoleucine (usually, not less than 10 mg/l) in a medium for growth.

Thus, viewing Claim 5 with this definition provided in the specification, it is apparent that Claim 5 requires culturing in bacterium. Thus, the claims require that the *Escherichia* bacterium produce L-glutamic acid (or L-proline or L-arginine) in excess of basal expression.

Accordingly, it is respectfully requested that this rejection be REVERSED.

(B) Claims 9-12 stand rejected under 35 U.S.C. §103(a) over Phillips et al in view of Integrated Enzyme Database and further in view of Kinoshita et al. This rejection is untenable and should not be sustained.

At the outset, Appellants submit that, for the reasons given above, Phillips et al fails to disclose or suggest collecting L-glutamic acid (L-proline or L-arginine) from the culture, as well as production and accumulation of L-glutamic acid (L-proline or L-arginine) beyond basal-level expression. Kinoshita et al discloses ion exchange and precipitation methods of isolation, but fails to compensate for the requisite level of production of L-glutamic acid.

In making this rejection on August 9, 2007, the Examiner alleged:

> "[I]t would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of producing glutamic acid in E. coli by collecting the accumulated product by using the conventional techniques of ion exchange and precipitation as taught by the Kinoshita et al. references for the expected benefit of

> obtaining the important amino acid glutamic acid useful in pharmaceutical and nutritional formulations."

As discussed above, Appellants submit that Phillips et al is silent about the production and accumulation of L-glutamic acid. In the Advisory Action mailed December 3, 2007, the Examiner alleges:

> "[I]t is noted that there is nothing on this record to demonstrate that any *Escherichia* or any *E. coli* that is L-isoleucine auxotrophic will have the ability to produce L-glutamic acid (or L-proline or L-arginine) beyond a basal level as argued. The claims as written merely require any *Escherichia* or any *E. coli* to be L-isoleucine auxotrophic and to have the ability to produce L-glutamic acid (or L-proline or L-arginine). The amount produced is not required to be beyond a basal level."

Appellants disagree with this allegation by the Examiner for the reasons give above. Specifically, it is submitted that Claim 5 requires "culturing an *Escherichia* bacterium... *to produce and accumulate* L-glutamic acid, L-proline or L-arginine in a culture" (*emphasis added*). As such, Appellants submit that the claims as presented *do* require expression beyond basal expression. Appellants submit that it is well known that the amount of L-glutamic acid (or L-proline or L-arginine) produced by an *E. coli* cell is only that which is sufficient to survive (i.e., basal production). Thus, in order to accumulate L-glutamic acid (or L-proline or L-arginine) in the culture as required by the pending claims, it is necessary that the *Escherichia* bacterium produce L-glutamic acid (or L-proline or L-arginine) in excess of basal expression.

Moreover, as defined on page 3, lines 15-21 of the specification, Appellants define the expression "a bacterium has ability to produce L-glutamic acid, L-proline or L-arginine" as follows:

> The expression "a bacterium has ability to produce L-glutamic acid, L-proline or L-arginine" means that the bacterium accumulates a significant amount of L-glutamic acid, L-proline or L-arginine in a medium when the bacterium is cultured in the medium, or increases the content of L-glutamic acid, L-proline or L-arginine in the bacterium. The expression "a

> bacterium is L-isoleucine auxotrophic" means that the bacterium requires L-isoleucine (usually, not less than 10 mg/l) in a medium for growth.

Thus, viewing Claim 5 with this definition provided in the specification, it is apparent that Claim 5 requires culturing in bacterium. Thus, the claims require that the *Escherichia* bacterium produce L-glutamic acid (or L-proline or L-arginine) in excess of basal expression.

The fact that Phillips et al is silent with respect to expression in excess of basal expression is dispositive of non-obviousness in this case.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*.

As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. §103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Determining the scope and content of the prior art; and

(B) Ascertaining the differences between the claimed invention and the prior art; and

(C) Resolving the level of ordinary skill in the pertinent art.

With respect to inquiry (A), Appellants submit that Phillips et al disclose a threonine dehydratase-less mutant (i.e., an isoleucine auxotroph) of *Escherichia coli* LA-9 (see Abstract and page 715, left column, paragraph 2). Phillips et al further disclose that isoleucine auxotrophy can be abolished by glutamate (see page 716, paragraph bridging the left and right columns). Kinoshita et al discloses that L-glutamic acid may be recovered from culture by ion exchange or precipitation (see Example 15).

As for inquiry (B), Appellants refer to the discussion above and submit that Phillips et al do not disclose or suggest collecting L-glutamic acid from the culture, as well as production and accumulation of L-glutamic acid beyond basal-level expression. Kinoshita et al do not disclose or suggest an *Escherichia* bacterium that is either L-isoleucine auxothropic or that expresses L-glutamic acid at a level beyond basal expression.

As for inquiry (C), the Examiner fails to offer any suggestion or assessment of the relative level of the skilled artisan. Appellants pose that the level of ordinary skill would be that of a basic lab researcher.

With the *Graham* factors resolved, the question of obviousness can be approached. The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006).

In this regard, Appellants submit that when combining the disclosures of Phillips et al and Kinoshita et al the artisan would, at best, be motivated to treat the bacteria of Phillips et al with either ion exchange or precipitation as disclosed by Kinoshita et al. However, it is well known that the amount of L-glutamic acid produced by an E. coli cell is only that which is sufficient to survive (i.e., basal production). Thus, even if the skilled artisan were to combine the disclosures of Phillips et al and Kinoshita et al they would not be motivated to collect L-glutamic acid from a culture in which L-glutamic acid is expected to exist at only a basal level. Moreover, even if this were the objective, *arguendo*, there would not be a reasonable expectation that sufficient levels of L-glutamic acid would be produced by the bacteria of Phillips et al. Accordingly, in absence of an explicit teaching as to greater than

basal production of L-glutamic acid, there is no motivation to apply the conventional techniques of ion exchange and precipitation to the culture of Phillips et al with an expectation that L-glutamic acid can be collected.

Further, there is not disclosure or suggestion in either Phillips et al or Kinoshita et al of how or any reason why the artisan would increase the level of L-glutamic acid production in the bacteria of Phillips et al. Integrated Enzyme Database merely provides the IntEnz Enzyme Nomenclature for EC 4.3.1.19.

In view of the foregoing, Appellants submit that the claimed invention is not obvious in view of the combined disclosures of Phillips et al, Integrated Enzyme Database, and Kinoshita et al.

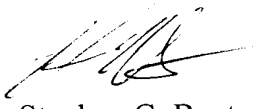
Accordingly, it is respectfully requested that this rejection be REVERSED.

VIII. CONCLUSION

For the above reasons, Claims 5-12 are *not* unpatentable under 35 U.S.C. §102(b) and under 35 U.S.C. §103(a), each over Phillips et al, Integrated Enzymy Database, and Kinoshita et al. Therefore, the Examiner's rejections should be REVERSED.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Attachments: Claims Appendix: Pending Claims in U.S. Application Serial No. 10/822,704
Evidence Appendix
Related Proceedings Appendix

CLAIMS APPENDIX

Pending Claims in U.S. Application Serial No. 10/822,704

1. – 4. (Canceled)

5. A method for producing L-glutamic acid, L-proline or L-arginine, which comprises culturing an *Escherichia* bacterium, which is L-isoleucine auxotrophic and has ability to produce L-glutamic acid, L-proline or L-arginine, in a medium containing L-isoleucine, to produce and accumulate L-glutamic acid, L-proline or L-arginine in a culture and collecting L-glutamic acid, L-proline or L-arginine from the culture.

6. The method according to Claim 5, wherein the *Escherichia* bacterium is deficient in any of L-isoleucine biosynthetic enzyme activities.

7. The method according to Claim 6, wherein the *Escherichia* bacterium is deficient in threonine deaminase activity.

8. (Previously Presented) The method according to Claim 5, wherein the *Escherichia* bacterium is *Escherichia coli*.

9. The method according to Claim 5, wherein said collecting L-glutamic acid, L-proline or L-arginine from the culture is performed by an ion exchange resin method, precipitation method or combination thereof.

10. The method according to Claim 6, wherein said collecting L-glutamic acid, L-proline or L-arginine from the culture is performed by an ion exchange resin method, precipitation method or combination thereof.

11. The method according to Claim 7, wherein said collecting L-glutamic acid, L-proline or L-arginine from the culture is performed by an ion exchange resin method, precipitation method or combination thereof.

12. The method according to Claim 8, wherein said collecting L-glutamic acid, L-proline or L-arginine from the culture is performed by an ion exchange resin method, precipitation method or combination thereof.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.